

Intramolecular Hydrogen-Bond Participation in Phosphonylammonium Salt Formation

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Supporting Information

Phenylphosphonic acid monoethyl ester (7). To a 0 °C solution of 90% phenylphosphonic dichloride **5** (1.0 mL, 6.35 mmol) in CH₂Cl₂ (25 mL) was added ethanol (1.12 mL, 19.04 mmol) followed by triethylamine (2.65 mL, 19.04 mmol) and the solution was stirred at r.t. for 1 h. The reaction was quenched with 1 M aq. HCl (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined org. extracts were dried (Na₂SO₄), evaporated *in vacuo*, and purified by flash chromatography (hexane/EtOAc 6:4) on silica gel to give phenylphosphonic acid diethyl ester as a colorless oil¹ (1.34 g, 99%): ¹H NMR (500 MHz, CDCl₃) δ 7.81-7.77 (m, 2 H), 7.52-7.50 (m, 1 H), 7.46-7.42 (m, 2 H), 4.15-4.03 (m, 4 H), 1.30 (t, *J* = 7.1 Hz, 6 H); ³¹P NMR (202.5 MHz, CDCl₃) δ 19.1.

A mixture of diester (1.0 g, 4.67 mmol) and 2 M aq. NaOH (50 mL) was stirred vigorously at r.t. for 20 h. The reaction mixture was washed with CH₂Cl₂ (50 mL), made acidic with 2 N H₂SO₄ (100 mL), and extracted with CH₂Cl₂ (3 x 100 mL). The combined org. extracts were dried (Na₂SO₄) and evaporated *in vacuo* to give **7** as a colorless oil² (839 mg, 97%): ¹H NMR (500 MHz, CDCl₃) δ 7.81-7.77 (m, 2 H), 7.51-7.49 (m, 1 H), 7.43-7.40 (m, 2 H), 4.09-4.03 (m, 2

H), 1.29 (t, $J = 7.1$ Hz, 3 H); ^{31}P NMR (202.5 MHz, CDCl_3) δ 21.5.

[(Benzyloxycarbonylmethylamino)methyl]phosphonic acid diethyl ester (20). To a solution of phosphonate diester **19** (500 mg, 1.66 mmol) in dry THF (10 mL) at 0 °C was added 95% sodium hydride (50 mg, 1.99 mmol). The solution was allowed to reach r.t., methyl iodide (114 μL , 1.83 mmol) was added, and the solution stirred for 5 h. The reaction mixture was quenched with 1 M aq. HCl (50 mL) and extracted with EtOAc (2 x 50 mL). The combined org. extracts were dried (Na_2SO_4), evaporated *in vacuo*, and purified by flash chromatography (hexane/EtOAc 50:50 to 25:75) on silica gel to give **20** as a colorless oil (345 mg, 66%): IR (CHCl_3) 3020 (m), 1720 (s), 1710 (s), 1250 (m), 1065 (s), 1045 (s) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.34-7.27 (m, 5 H), 5.12 (s, 2 H), 4.13-4.00 (m, 4 H), 3.74-3.68 (m, 2 H), 3.04 (s, 3 H), 1.29-1.22 (m, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ [156.13 + 155.57], [136.50 + 136.25], 128.39, [128.08 + 127.97], 127.77, [67.60 + 67.47], [62.24 + 62.19], [44.56 + 44.46] (d, $J_{\text{CP}} = 160$ Hz), [35.84 + 35.36], [16.31 + 16.26]; ^{31}P NMR (202.5 MHz, CDCl_3) δ [23.1 + 22.6]; high-resolution mass spectrum (ES) m/z 338.1132 [(M+Na) $^+$; calcd for $\text{C}_{14}\text{H}_{22}\text{NO}_5\text{PNa}$: 338.1133].

[(Benzyloxycarbonylmethylamino)methyl]phosphonic acid monoethyl ester (21a). A mixture of diester **20** (160 mg, 0.51 mmol) and 2 M aq. NaOH (10 mL) was vigorously stirred at r.t. for 18 h. The reaction mixture was washed with CH_2Cl_2 (10 mL), acidified with 2 M aq. H_2SO_4 (20 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The combined org. extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give **21a** as a colorless oil (101 mg, 69%): IR (CHCl_3) 3040 (s), 1730 (s), 1710 (s), 1440 (m) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.12 (br s, 1 H), 7.35-7.27 (m, 5 H), 5.12 (s, 2 H), 4.11-4.01 (m, 2 H), 3.74-3.68 (m, 2 H), 3.04 (s, 3 H), 1.28-1.22 (m, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ [156.39 + 155.79], 136.43, 128.45, 128.02, 127.82, 67.65, [62.42 + 62.13], 44.89 (d, $J_{\text{CP}} = 160$ Hz), [35.91 + 35.42], [16.27 + 16.22]; ^{31}P NMR (202.5 MHz, CDCl_3) δ [24.6 + 24.5]; high-resolution mass spectrum (ES) m/z 310.0830 [(M+Na) $^+$; calcd for

C₁₂H₁₈NO₅PNa: 310.0820].

[[(9-*H*-Fluoren-9-ylmethoxycarbonyl)methylamino]methyl}phosphonic acid monoethyl ester (21b). A solution of monoester **20a** (137 mg, 0.48 mmol) in ethanol (25 mL) was treated with 10% Pd/C (10 mg) under hydrogen atmosphere for 5 h. The reaction mixture was filtered and evaporated *in vacuo*. The residue was dissolved in CHCl₃, cooled to 0 °C, and treated with 9-fluorenylmethyl chloroformate (136 mg, 0.53 mmol) and stirred for 30 min. Triethylamine (100 µL, 0.72 mmol) was added dropwise, the solution was allowed to warm to r.t. and stirred for 20 h. The reaction was quenched with 1 M aq. HCl (20 mL) and extracted with CH₂Cl₂ (20 mL). The organic phase was dried (Na₂SO₄), evaporated *in vacuo*, and purified by flash chromatography (CHCl₃/MeOH 90:10 to 75:25) on silica gel to give **21b** as a colorless sticky solid (83 mg, 46%): IR (CHCl₃) 1700 (m), 1680 (m), 1460 (w), 1300 (w), 1220 (m), 1090 (m), 1060 (m) cm⁻¹; ¹H NMR (500 MHz, (CD₃)₂SO) δ 7.87 (d, *J* = 7.5 Hz, 2 H), 7.67-7.60 (m, 2 H), 7.40-7.37 (m, 2 H), 7.32-7.29 (m, 2 H), 4.28-4.25 (m, 3 H), 3.78-3.75 (m, 2 H), 3.38 (d, *J* = 10.5 Hz, 2 H), 2.91 (s, 3 H), 1.06 (t, *J* = 6.9 Hz, 3 H); ¹³C NMR (125 MHz, (CD₃)₂SO) δ [155.42 + 155.21], 143.83, 140.68, 127.53, 126.99, 124.87, 120.01, 79.10, 66.69, 59.35, 46.62, 34.57, 16.58; ³¹P NMR (202.5 MHz, CDCl₃) δ 18.0; high-resolution mass spectrum (ES) *m/z* 374.1676 [(M-H)⁺; calcd for C₁₉H₂₁NO₅P: 374.1157].

[2-(*N*-Acetyl)aminophenyl]phosphonic acid diethyl ester (25).³ A solution of diester **24** (2.50 g, 9.65 mmol) in ethanol (100 mL) was treated with 10% Pd/C (100 mg) under hydrogen atmosphere for 15 h. The reaction mixture was filtered over Celite, evaporated *in vacuo*, and purified by flash chromatography (hexane/EtOAc 6:4) on silica gel to give (2-aminophenyl)phosphonic acid diethyl ester as a yellow oil (1.76 g, 80%): ¹H NMR (500 MHz, CDCl₃) δ 7.42 (dd, *J* = 14.4, 7.7 Hz, 1 H), 7.26-7.22 (m, 1 H), 6.68 (dt, *J* = 7.5, 3.3 Hz, 1 H), 6.63 (t, *J* = 7.5 Hz, 1 H), 5.25 (br s, 2 H), 4.15-3.99 (m, 4 H), 1.30 (t, *J* = 7.2 Hz, 6 H); ³¹P NMR (202.5

MHz, CDCl₃) δ 21.7.

To a solution of aminophosphonate (1.70 g, 7.42 mmol) and 4-dimethylaminopyridine (1.09 g, 8.91 mmol) in CH₂Cl₂ (50 mL) was added dropwise acetyl chloride (581 μ L, 8.17 mmol) and the solution was stirred at r.t. for 30 min. The reaction was quenched with 1 M aq. HCl (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined org. extracts were dried (Na₂SO₄), evaporated *in vacuo*, and purified by flash chromatography (hexane/EtOAc 50:50) on silica gel to give **25** as a colorless oil (1.79 g, 89%): ¹H NMR (500 MHz, CDCl₃) δ 8.57 (t, *J* = 7.5 Hz, 1 H), 7.55-7.49 (m, 2 H), 7.08 (dt, *J* = 7.5, 3.1 Hz, 1 H), 4.16-3.99 (m, 4 H), 2.18 (s, 3 H), 1.30 (t, *J* = 7.0 Hz, 6 H); ³¹P NMR (202.5 MHz, CDCl₃) δ 20.1.

[2-(*N*-Acetyl)aminophenyl]phosphonic acid monoethyl ester (26). A mixture of diester **25** (1.21 g, 4.46 mmol) and 2 M aq. NaOH (100 mL) was vigorously stirred at r.t. for 2 h. The reaction mixture was washed with CH₂Cl₂ (50 mL), acidified with 2 M aq. H₂SO₄ (120 mL), and extracted with CH₂Cl₂ (3 x 50 mL). The combined org. extracts were dried (Na₂SO₄) and evaporated *in vacuo* to give **26** as a yellow sticky solid (582 mg, 54%): IR (CHCl₃) 3020 (w), 1710 (m), 1620 (m), 1600 (s), 1550 (m), 1450 (s), 1320 (s), 1050 (s), 1000 (m) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.65 (s, 1 H), 8.36-8.22 (m, 1 H), 7.66 (dd, *J* = 14.9, 7.6 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 7.13-7.09 (m, 1 H), 4.01-3.96 (m, 2 H), 2.09 (s, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 169.10, 140.93 (d, *J*_{CP} = 6 Hz), 133.85, 132.57 (d, *J*_{CP} = 7 Hz), 123.52 (d, *J*_{CP} = 14 Hz), 121.74 (d, *J*_{CP} = 10 Hz), 115.80 (d, *J*_{CP} = 183 Hz), 62.61 (d, *J*_{CP} = 6 Hz), 24.69, 16.05 (d, *J*_{CP} = 7 Hz); ³¹P NMR (202.5 MHz, CDCl₃) δ 20.9; high-resolution mass spectrum (ES) *m/z* 310.0830 [(M+Na)⁺; calcd for C₁₂H₁₈NO₅PNa: 310.0820].

(2-Oxo-1,4-dihydro-2H-benzo[1,3]oxazin-8-yl)phosphonic acid diethyl ester (28). A solution of ester **27** (470 mg, 1.70 mmol), sodium borohydride (322 mg, 8.48 mmol) and zinc chloride (577 mg, 4.24 mmol) in THF (20 mL) was heated at reflux for 2 h. The reaction mixture

was allowed to cool down, carefully quenched with a sat. aq. NaCl solution (30 mL), and extracted with EtOAc (3 x 30 mL). The combined org. extracts were dried (Na₂SO₄), evaporated *in vacuo*, and purified by flash chromatography (hexane/EtOAc/Et₃N 80:19:1) on silica gel to give (2-amino-3-iodophenyl)methanol as a colorless solid (380 mg, 90%): mp 120-121 °; IR (CHCl₃) 3015 (m), 1616 (s), 1453 (s), 1226 (m), 1207 (s), 998 (m) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.61 (d, *J* = 7.9 Hz, 1 H), 7.05 (d, *J* = 7.4 Hz, 1 H), 6.44-6.41 (m, 1 H), 4.65 (s, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 146.42, 139.14, 129.29, 124.81, 119.25, 85.90, 65.04; ES-MS *m/z* 249 [50, M⁺], 232 [100, (M-OH)⁺]; Anal. Calcd for C₇H₈INO: C, 33.76; H, 3.24; N, 5.62. Found: C, 33.77; H, 3.25; N, 5.57.

To a solution of (2-amino-3-iodophenyl)methanol (100 mg, 0.40 mmol) and 1,1'-carbonyldiimidazole (78 mg, 0.48 mmol) in THF (5 mL) at 0 °C was added 60% sodium hydride (16 mg, 0.40 mmol) and the solution was stirred at 0 °C for 30 min. The reaction was quenched with 1M aq. HCl solution (20 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined org. extracts were dried (Na₂SO₄), evaporated *in vacuo*, and purified by flash chromatography (hexane/EtOAc 8:2) on silica gel to give 8-iodo-1,4-dihydrobenzo[1,3]oxazin-2-one as a colorless solid (83 mg, 75%): mp 119-121 °; IR (CHCl₃) 3024 (m), 3018 (s), 1745 (s), 1724 (m), 1480 (m), 1224 (s), 1212 (s) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.68 (d, *J* = 8.0 Hz, 1 H), 7.22 (br s, 1 H), 7.08 (d, *J* = 7.5 Hz, 1 H), 6.82-6.79 (m, 1 H), 5.24 (s, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 151.83, 138.57, 136.48, 124.76, 124.48, 119.38, 82.49, 68.51; high-resolution mass spectrum (ES) *m/z* 275.9515 [(M+H)⁺; calcd for C₈H₇INO₂: 275.9522].

A solution of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (12 mg, 0.015 mmol) and triethylsilane (5 µL, 0.03 mmol) in toluene (1 mL) was degassed and heated at 50 °C in a sealed tube for 10 min. A degassed solution of 8-iodo-1,4-dihydrobenzo[1,3]oxazin-2-one (40 mg, 0.15 mmol), diethylphosphite (37 µL, 0.29 mmol) and triethylamine (40 µL, 0.29 mmol) in toluene (1 mL) was then added under argon and the mixture heated at 50-60 °C for 2.5 h. The reaction mixture was evaporated *in vacuo* and purified by flash

chromatography (hexane/EtOAc 75:25 to 50:50) on silica gel to give **28** as a colorless solid (33 mg, 80%): mp 84-85°; IR (CHCl₃) 3016 (m), 1725 (s), 1601 (m), 1456 (m), 1257 (m), 1214 (m), 1051 (m), 1019 (s) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.70 (s, 1 H), 7.51 (dd, *J* = 13.9, 7.7 Hz, 1 H), 7.26 (d, *J* = 7.4 Hz, 1 H), 7.10-7.06 (m, 1 H), 5.25 (s, 2 H), 4.19-4.03 (m, 4 H), 1.31 (t, *J* = 7.1, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 151.16, 140.04, 132.52 (d, *J*_{CP} = 6 Hz), 128.77 (d, *J*_{CP} = 3 Hz), 122.43 (d, *J*_{CP} = 14 Hz), 119.11 (d, *J*_{CP} = 12 Hz), 111.13 (d, *J*_{CP} = 184 Hz), 67.86, 62.77 (d, *J*_{CP} = 5 Hz), 16.20 (d, *J*_{CP} = 6 Hz); ³¹P NMR (202.5 MHz, CDCl₃) δ 17.6; high-resolution mass spectrum (ES) *m/z* 286.0844 [(M+H)⁺; calcd for C₁₂H₁₆NO₅P: 286.0844].

(2-Oxo-1,4-dihydro-2*H*-benzo[1,3]oxazin-8-yl)phosphonic acid benzyl ester ethyl ester (29). A solution of [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium (II) complex with dichloromethane (3 mg, 0.004 mmol) and triethylsilane (1 μL, 0.01 mmol) in toluene (1 mL) was degassed and heated in a sealed tube at 50 °C for 15 min. A degassed solution of iodide 8-iodo-1,4-dihydrobenzo[1,3]oxazin-2-one (10 mg, 0.04 mmol), benzylethylphosphite (15 mg, 0.07 mmol) and triethylamine (28 μL, 0.07 mmol) in toluene (1 mL) was then added under argon and the mixture heated at 50-60 °C for 2 h. The reaction mixture was evaporated *in vacuo* and purified by flash chromatography (CH₂Cl₂/EtOAc 95: to 70:30) on silica gel to give **29** as a colorless oil (11 mg, 87%): IR (CHCl₃) 3018 (m), 1725 (m), 1601 (w), 1456 (w), 1256 (w), 1222 (s), 1207 (s), 1044 (w), 1014 (w) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.66 (s, 1 H), 7.48 (dd, *J* = 13.4, 7.1 Hz, 1 H), 7.30-7.27 (m, 5 H), 7.23 (d, *J* = 7.5 Hz, 1 H), 7.05-7.01 (m, 1 H), 5.22 (s, 2 H), 5.13 (dd, *J* = 11.7, 9.5 Hz, 1 H), 5.01 (dd, *J* = 11.7, 7.8 Hz, 1 H), 4.19-4.07 (m, 2 H), 1.31 (t, *J* = 7.1, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 151.09, 139.93 (d, *J*_{CP} = 9 Hz), 135.27 (d, *J*_{CP} = 6 Hz), 132.50 (d, *J*_{CP} = 6 Hz), 128.76 (d, *J*_{CP} = 3 Hz), 128.58, 128.51, 128.08, 122.37 (d, *J*_{CP} = 14 Hz), 119.14 (d, *J*_{CP} = 13 Hz), 110.90 (d, *J*_{CP} = 184 Hz), 68.20 (d, *J*_{CP} = 5 Hz), 67.78, 62.89 (d, *J*_{CP} = 6 Hz), 16.15 (d, *J*_{CP} = 6 Hz); ³¹P NMR (202.5 MHz, CDCl₃) δ 18.0.

(2-Oxo-1,4-dihydro-2H-benzo[1,3]oxazin-8-yl)phosphonic acid monoethyl ester

(30). A solution of phosphonate **29** (7 mg, 0.02 mmol) in ethanol (2 mL), was treated with 10% Pd/C (1 mg) under a hydrogen atmosphere for 1 h. The reaction mixture was filtered and evaporated *in vacuo* to give **30** as a colorless sticky solid (5 mg, 97%): IR (CHCl₃) 3019 (s), 1716 (m), 1600 (m), 1455 (m), 1272 (w), 1223 (s), 1043 (m) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.13 (s, 1 H), 7.61-7.56 (m, 1 H), 7.22-7.20 (m, 1 H), 7.07-7.04 (m, 1 H), 5.23 (s, 2 H), 4.00-3.94 (m, 2 H), 1.28 (t, *J* = 6.5, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 151.50, 138.65 (d, *J*_{CP} = 7 Hz), 132.80 (d, *J*_{CP} = 6 Hz), 128.67, 122.71 (d, *J*_{CP} = 14 Hz), 119.04 (d, *J*_{CP} = 12 Hz), 112.23 (d, *J*_{CP} = 189 Hz), 68.03, 62.70 (d, *J*_{CP} = 5 Hz), 16.11 (d, *J*_{CP} = 6 Hz); ³¹P NMR (202.5 MHz, CDCl₃) δ 18.4.

(2-Oxo-1,4-dihydro-2H-benzo[1,3]oxazin-6-yl)phosphonic acid benzyl ester ethyl ester (33).

mp 135-136°; IR (CHCl₃) 3040 (s), 2400 (m), 1760 (m), 1740 (m), 1600 (m), 1520 (m), 1220 (s), 1120 (m), 1060 (m), 1040 (m), 940 (m) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.98 (s, 1 H), 7.68 (dd, *J* = 12.9, 8.1 Hz, 1 H), 7.58 (d, *J* = 12.9 Hz, 1 H), 6.95 (dd, *J* = 8.1, 2.8 Hz, 1 H), 5.33 (s, 2 H), 4.15-4.03 (m, 4 H), 1.30 (t, *J* = 7.1, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 152.87, 139.55 (d, *J*_{CP} = 3 Hz), 133.02 (d, *J*_{CP} = 10 Hz), 128.09 (d, *J*_{CP} = 12 Hz), 122.68 (d, *J*_{CP} = 195 Hz), 117.98 (d, *J*_{CP} = 16 Hz), 114.31 (d, *J*_{CP} = 16 Hz), 68.22, 62.25 (d, *J*_{CP} = 5 Hz), 16.25 (d, *J*_{CP} = 6 Hz); ³¹P NMR (202.5 MHz, CDCl₃) δ 18.3; ES-MS *m/z* 308 [20, (M+Na)⁺], 349 [100, (M+Na+MeCN)⁺]; Anal. Calcd for C₁₂H₁₆NO₅P: C, 50.53; H, 5.65; N, 4.91. Found: C, 50.50; H, 5.72; N, 4.88.

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